Risk of SARS-CoV-2 testing, PCR-confirmed infections and COVID-19--related hospital admissions in children and young people: birth cohort study

Pia Hardelid,[1†] Graziella Favarato,[1] Linda Wijlaars,[1] Lynda Fenton,[2] Jim McMenamin,[3] Tom Clemens,[4] Chris Dibben,[4] Ai Milojevic,[5] Alison Macfarlane,[6] Jonathon Taylor,[7] Steven Cunningham,[8*] Rachael Wood.[9*]

[1]Population, Policy and Practice Research and Teaching Department, University College London Great Ormond Street Institute of Child Health, London, UK

[2]Clinical and Public Health Intelligence Team, Public Health Scotland, Edinburgh, UK

[3]Public Health Scotland, Respiratory Infection Team, Glasgow, UK

[4]School of Geosciences, The University of Edinburgh, Edinburgh, UK

[5]Department of Public Health, Environments and Society, London School of Hygiene & Tropical Medicine, London, UK

[6]Centre for Maternal and Child Health Research, City, University of London, London, UK

[7]Faculty of Built Environment, Tampere University, Tampere, Finland

[8]Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK

[2,9]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

**Joint last authors

[†]Corresponding author. Address for correspondence: [1]Population, Policy and Practice Research and Teaching Department, University College London Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK. p.hardelid@ucl.ac.uk

Abstract

Background

There have been no population-based studies of SARS-CoV-2 testing, PCR-confirmed infections and COVID-19-related hospital admissions across the full paediatric age range. We examine the epidemiology of SARS-CoV-2 in children and young people (CYP) aged <23 years.

Methods

We used a birth cohort of all children born in Scotland since 1997, constructed via linkage between vital statistics, hospital records and SARS-CoV-2 surveillance data. We calculated risks of tests and PCR-confirmed infections per 1000 CYP-years between August and December 2020, and COVID-19-related hospital admissions per 100,000 CYP-years between February and December 2020. We used Poisson and Cox proportional hazards regression models to determine risk factors.

Results

Among the 1226855 CYP in the cohort, there were 378402 tests, 19005 PCR confirmed infections and 346 admissions, corresponding to rates of 770.8/1000 (95% confidence interval 768.4-773.3), 179.4 (176.9-182.0) and 29.4/100,000 (26.3-32.8) CYP-years respectively. Infants had the highest COVID-19-related admission rates. Chronic conditions, particularly multiple types of conditions, was strongly associated with COVID-19-related admissions across all ages. The hazard ratio for >1 chronic condition type was 12.2 (7.9-18.82) compared to children with no chronic conditions. 89% of admitted children had no chronic conditions recorded.

Conclusions

Infants, and CYP with chronic conditions are at highest risk of admission with COVID-19, however the majority of admitted CYP have no chronic conditions. These results provide evidence to support risk/benefit analyses for paediatric COVID-19 vaccination programmes. Studies examining whether maternal vaccine during pregnancy prevents COVID-19 admissions in infants are urgently needed.

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Background

Children are much less likely to experience hospital admission and mortality related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection than adults.[1] In Europe in 2020, 1.7% of COVID-19-related hospital admissions were in children <19 years of age.[2]

Whilst early reports during the spring and summer of 2020 indicated less than 5% of SARS-CoV-2 positive cases in the United States,[3] China[4] and Spain[5] were in children, the epidemiology has changed over time and place, particularly in association with vaccination policy and access, with children under 10 years of age being the dominant population infected in the latter part of 2021 in the UK..[6]

Over the course of the pandemic our understanding of how SARS-CoV-2 infection affects children has also improved. Children who experience more severe symptoms of SARS-CoV-2 may present with acute infection symptoms such as fever, cough, shortness of breath, nausea/vomiting, or upper respiratory symptoms.[7-9] Children may also present with an acute inflammatory syndrome, paediatric inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS; also referred to as multisystem inflammatory syndrome related to COVID - MIS-C), several weeks after initial infection.[10-12] Children aged <2 years old appear to be over-represented among children admitted to hospital with acute symptoms of SARS-CoV-2 infection, whereas children aged 10 years or older account for the largest proportion of admitted PIMS-TS cases.[8 13]

Two preprints indicate that among children admitted to hospital with SARS-CoV-2 or PIMS-TS, those with specific chronic respiratory, neurological, gastrointestinal or cardiovascular conditions, and particularly children with multiple comorbidities, were at increased risk of Paediatric Intensive Care Unit (PICU) admission or death. Infants and teenagers appeared to have higher odds of these severe outcomes compared to children aged 1-4 years old.[14 15] A lower reported risk of severe disease and, until 2021, relatively lower rates of infection in children have supported a narrative that the benefits and risks (primarily of myocarditis following second dose mRNA vaccines in young men[16 17]) of vaccinations in children are finely balanced.

Most studies of paediatric SARS-CoV-2 infection have been case series of infected or hospitalised children, making calculations of population-based risks of confirmed infections and associated admissions among different groups of children, including children with chronic conditions, impossible. A recent study presented population-based risks of COVID-

19-related admission for children with asthma, indicating an increased risk that supports vaccine strategies targeted to this group.[18] Our aim was to provide population based estimates of risk of SARS-CoV-2 testing, PCR confirmed infections and COVID-19 related admissions in children and young people (CYP) based on age, presence of multiple chronic conditions, and socioeconomic status, that could support vaccination and other policy recommendations across the whole paediatric population.

Methods

Data sources

We used a national birth cohort of all children and young people (CYP) born in Scotland from 1997 onwards, developed from administrative health datasets linked to public health surveillance data on SARS-CoV-2 test results, originally constructed for the PICNIC study.[19] CYP born in 1997 onwards were included. Birth registrations comprised the cohort spine, and CYP are linked over time and between databases using the Community Health Index (CHI) number, a unique personal identifier recorded at all interactions with the Scottish National Health Service (NHS). Table 1 summarises the databases and variables used in this study.

110 **Table 1. Datasets and variables from the national Scottish birth cohort used in the**
111 **study**

Dataset	Dataset details	Variables used
National Records for Scotland (NRS) birth registrations	Vital registration data on all children born in Scotland and their parents, collected via registry offices	Week and year of birth; Baby Sex; Socio-economic position (parents' occupation at birth).
Scottish Morbidity Record (SMR)-01	Contains data on post-neonatal admissions and day cases to all NHS hospitals in Scotland	Admission and discharges dates; Primary and secondary diagnoses during admission; Type of hospital admission; Admission and discharge data from Intensive Care Unit (ICU).
SMR-02 (maternity records)	Contains data on all maternity admissions (including deliveries) in Scotland	Estimated gestational age; birth weight; number of older siblings (parity).
COVID-19 Tests	Contains data on all PCR- and antigen tests for SARS-Cov-2 with results and dates	Date of testing; Type of test; Result.
National Records for Scotland (NRS) death registrations	Vital registration data on children who died in Scotland	Date of death; Cause of death.
Scottish Birth Records (SBR)	Contains data on all children born in NHS hospitals, with data on neonatal admissions in and after April 2003	Diagnoses recorded at or shortly after birth ; Primary and secondary diagnoses at birth admission.
CHI register	Contains data on migration in/out Scotland	Migration outside Scotland.
Child Health Surveillance Programme-School	Contains data school health visits	Height and weight at age 5

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Study population and follow-up

We included CYP born in Scotland from 1st April 1997 to 31st December 2020. Children born at less than 24 completed weeks' gestation or with a birthweight <500 grammes were excluded to ensure stillbirths were not inadvertently included.[20] CYP whose mothers were not resident in Scotland at the time of delivery, and CYP who migrated out of Scotland before 1st February 2020 were also excluded. For analyses of SARS-CoV-2 tests and positive test results (from now on referred to PCR-confirmed infections), CYP were followed from birth or the 1st August 2020 (whichever occurred last), until death, migration from Scotland, or their 23rd birthday, whichever occurred first. 1st August 2020 was chosen as the follow-up start date for analyses of tests and PCR-confirmed infections since this is when testing for SARS-CoV-2 became commonly available in the community (rather than solely in hospitals) for children of all ages.[21] For calculation and analyses of rates of COVID-19-related admissions, we used the follow-up start date as the 1st February 2020. This allowed us to include all COVID-19-related hospital admissions since PCR testing for SARS-CoV-2 was available for suspected cases in hospital from January 2020.

Outcomes

Our primary outcomes were rates of a) SARS-CoV-2 PCR tests (positive or negative); b) PCR-confirmed SARS-CoV-2 infections; c) COVID19-related hospital admissions. We also considered as secondary outcomes d) PIMS-TS admissions and e) COVID19-related intensive care unit (ICU) stays.

For a), we included all SARS-CoV-2 PCR tests recorded between1st August 2020 and 31st December 2020 in the COVID19 Tests Dataset. The samples were collected in hospitals, primary care, via national testing centres, or self-collection via home test kits. We did not include antigen (lateral flow device) test results, as they were not comprehensively represented in the COVID19 Tests dataset during 2020 (only 5% of test results in the cohort during the study period were from lateral flow devices). We defined as duplicate tests multiple tests taken on the same day, in the same CYP, with the same result, irrespective of whether they were taken at different locations. All duplicate tests, whether positive or negative, were excluded when calculating testing rates. For b), a PCR-confirmed SARS-CoV-2 infection was defined as the first record of a positive SARS-CoV-2 PCR test result (the index positive test) recorded in the COVID19 Tests dataset between1st August 2020 and 31st December 2020. Public Health Scotland recommends excluding all repeat positive tests within 90 days of the index positive sample date, and less than 5 CYP had multiple positive results beyond this time period. Therefore, only the first positive SARS-CoV-2 PCR test

result for each child was included when calculating rates of PCR-confirmed SARS-CoV-2 infections, and identifying COVID-19-related hospital admissions.

We included all COVID-19-related hospital admissions (outcome c) between 1st February and 31st December 2020. To define COVID-19 related hospital admissions, we first linked episodes in the hospital admission dataset (Scottish Morbidity Record-01; Table 1) into admissions by assuming that episodes where the difference between the admission date and previous discharge date was ≤1 day[22] indicated the same admission. Second, we identified COVID-19 related admissions where: (i) an individual had tested positive for SARS-CoV-2 up to 14 days prior to hospital admission, on the day of admission, or in between the hospital admission and discharge date, and/or (ii) an International Classification of Diseases-version 10 (ICD-10) diagnostic code for COVID-19 (U07.1 – U07.2) had been recorded during an admission as a primary or secondary diagnosis.

Since the ICD-10 code for PIMS-TS (U07.5) was introduced at the end of the follow-up period, we used other ICD-10 codes indicating systemic inflammatory response syndrome of infectious origin without organ failure (R65X), cardiogenic shock (R57X) or other specified systemic involvement of connective tissue (M35.8), suggestive of PIMS-TS recorded during an admission which had a positive SARS-CoV-2 PCR test within 28 day prior to the admission date.

A COVID-19-related intensive care unit (ICU) stay (outcome e) was defined where a child had an SMR-01 episode with 'significant facility' recorded with a positive SARS-CoV-2 PCR test to 21 days prior to the start of, or during, the ICU stay. ICU episodes where the difference between the ICU admission date and previous ICU discharge date was ≤1 day were assumed to indicate the same ICU stay.

Risk factors

We examined four risk key factors for outcomes a-c): age group, sex, family socio-economic position (SEP) and history of chronic conditions. Age group was defined on 1st February 2020 as the following five categories: <1 year (this also includes children born during 2020), 1-4 years, 5-11 years, 12-17 years and 18-22 years. We chose these age groups to reflect likely mixing patterns based on age (i.e. prior to formal childcare, nursery/preschool, primary school, secondary school, and higher/further education or work). Sex was recorded on the birth record. Family SEP was defined using parents' (father's, or mother's if the birth was not jointly registered) occupation recorded on birth registration. This was coded using the UK National Statistics Socio-economic Classification (NS-SEC).[23] We collapsed the NS-SEC

classes into three groups: high SEP (managerial and professional occupations), middle SEP (intermediate occupations) and low SEP (routine and manual occupations). We identified history of chronic conditions by examining ICD-10 diagnostic codes recorded in SMR-01 in the previous five years. For children aged less than five years old at the start February 2020 or born during 2020, we used all available SMR-01 data and any diagnoses recorded on Scottish Birth Records. The code list for identifying chronic conditions was developed by Hardelid et al;[24] and classifies chronic conditions into 8 types depending on body system: developmental/mental health, blood/cancer, chronic infections, respiratory, metabolic/gastrointestinal/endocrine/genitourinary, musculoskeletal/skin neurological/sensory, and cardiac conditions. We grouped the history of chronic conditions as none, one type of condition, and more than type of chronic condition.

We further explored whether gestational age and the number of older siblings affected outcomes b) and c) in children aged <5 years, and BMI in CYP aged 5-17, after adjusting for the four key risk factors. Gestational age was coded into a binary variable: preterm (<37 weeks) and term/late term (≥37 weeks). Number of older siblings (indicated by parity recorded on maternity records) was grouped into a three-category variable: no older siblings, one older sibling and two or more older siblings. BMI was derived from the Child Health Surveillance Programme -School dataset, which includes height and weight measurements for children starting their first (reception) year at primary school (at age 5 years), categorised using the British 1990 growth reference standards[25] as underweight (<5th percentile), healthy weight (5th to <85th percentile) and overweight/obese (≥85th percentile).

Statistical analyses

We calculated rates of outcomes a) and b) per 1,000 CYP years and outcome c) per 100,000 CYP-years with 95% confidence intervals, according to each of the risk factors. We estimated the median length of stay with interquartile ranges (IQRs) for COVID-19 related hospital admissions.

We examined the association between risk factors and testing rates using Poisson regression models with robust standard errors to account for multiple tests per child. To examine the association between risk factors and PCR-confirmed SARS-CoV-2 infection, and COVID19-related admission risk we used Cox proportional hazards regression models. Where a child had multiple COVID-19-related admissions, only the first was included in the Cox proportional hazards models. For each primary outcome, we first fitted an overall model including all ages. We included age group, sex, SEP and history of chronic conditions a priori as risk factors in the main model. We tested for interaction with age group and each of

the other main risk factors using the Wald test. Two-sided *p*-values <0.05 were considered statistically significant.

Based on these results, we then fitted models for each primary outcome stratified by age group if a statistically significant interaction with age was identified for any of the other variables or if we identified non-proportional hazards. In further analyses for ages <5 years old we included parity and gestational age as additional risk factors in the models; and for ages 5-17 years we included BMI category. We tested the proportional hazards assumption of the Cox model by inspecting plots of Schoenfeld residuals[26] and survival curves according to each main risk factors.

As there was only a small number of events for our secondary outcomes, we did not carry out detailed statistical analyses. We report the number of cases, median length of stay and age (with IQRs) for these outcomes.

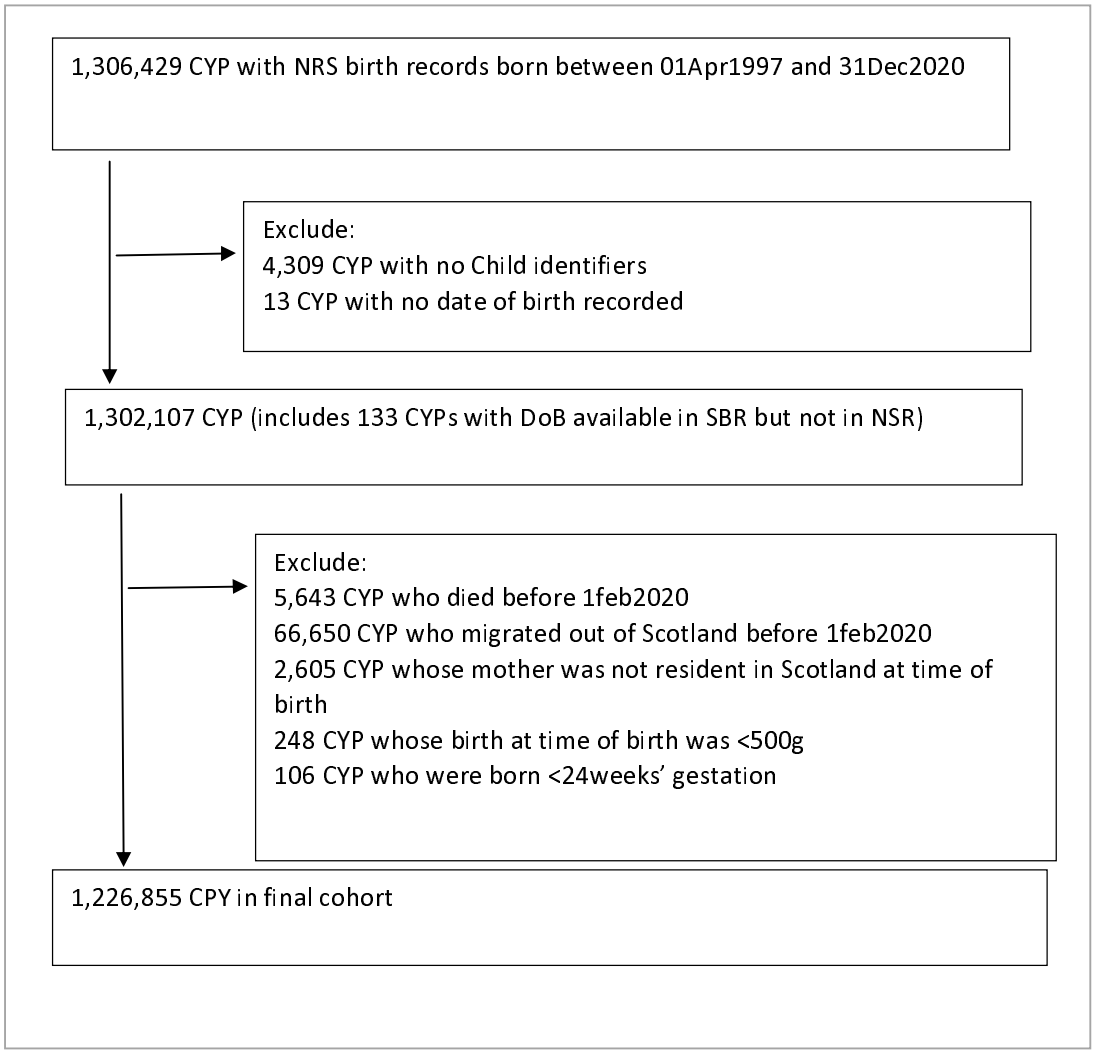
All analyses were based on complete cases, as only a small number of CYP and missing values for any of the main variables. All statistical analyses were performed using Stata 16.0.

Sensitivity analyses

We repeated the analyses for outcome c) using a more specific definition of a COVID-19-related admission restricted to emergency admissions with U07.1 or U07.2[27] as the primary diagnosis.

Results

This study included 1,226,855 CYP (Figure 1). Baseline characteristics of the participants are presented in Table 2. The median age on February 2020 was 11 years (IQR 5-17), and 5.4% of the cohort (66,974/1,226,855 CYP) had at least one chronic condition recorded in their hospital or birth record in the previous five years.



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241 **Figure 1** Flow chart describing creation of the final cohort

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TABLE 2 Cohort baseline characteristics (*n*=1,226,855)

	Number	%
Sex		
Male	628,410	51.2
Female	598,445	48.8
missing	*0*	*0*
Age (years)*		
Median 10.8 (IQR 5-17) yr		
<1 yr	92,539	7.5
1-4 yr	206,677	16.9
5-11 yr	326,455	26.6
12-17 yr	358,195	29.2
18-22 yr	242,989	19.8
Missing	*0*	*0*
Socio economic position**		
High	136,938	11.2
Middle	582,342	47.5
Low	507,563	41.4
Missing	*12*	*0*
Chronic conditions***		
None	1,159,878	94.5
One	59,972	4.9
More than one type	7,005	0.6
Gestational age (weeks) (aged* <5yr, *n*=292,289)		
Pre-term (<37 weeks)	23,825	8.0
Normal/Post-term (≥37 weeks)	268,464	89.7
Missing	*6,927*	*2.3*
Number of older siblings (aged*<5yr, *n*=289,800)		
None	124,289	41.5
One	102,944	34.4
Two or more	62,567	20.9
Missing	*9,416*	3.2
BMI *** (aged* 5-17, *n*=550,874)		
Underweight	8,930	1.30
Normal	421,182	60.2
Overweight/Obese	120,762	17.6
missing	*142,776*	*20.9*

* As on 1st February 2020; aged<1yr includes those born between 1 Feburary2020 and 31 December 2020. ** From UK National Statistics Socio-economic Classification (NS-SEC): SEP (managerial and professional occupations), middle SEP (intermediate occupations), low SEP (routine and manual occupations). ***Includes any chronic conditions recorded in the hospital records in the previous five years. ***As recorded in the Child Health Surveillance Programme-School at aged 5 and standardised according to the British 1990 growth reference standards (Cole 1998): underweight (<5th percentile), normal weight (5th to <85th percentile), overweight/obese (≥85th percentile).

SARS-CoV-2 testing

Between 1st August (week 31) to 31st December 2020 (week 52) we identified 378,402 PCR tests linked to 256,741 CYP; hence 20.9% of CYP in the cohort had at least one test. Figure 2 shows the weekly number of PCR tests by age group. The majority of CYP had been tested only once (200,288; 78.0%); 40,188 (15.7%) had been tested twice and 16,265 (6.3%) more than twice.

The crude testing rate was 770.8 (95%CI 768.4-773.3) per 1,000 CYP-years. Testing rates varied by age group and chronic conditions: children aged 1-4 years, young adults (age 18-22 years), and those with more than one chronic condition recorded had the highest testing rates (Appendix Table 1 & 2). Children aged <5 years born preterm were also more likely to be tested compared to children born at term (Appendix Table 3).

Models that mutually adjusted for all four main predictors suggested increasing age (and particularly an age of 18-22 years) and a history of chronic conditions were strongly associated with being tested (Table 3). As there was a statistically significant interaction term between age group and each of the other risk factors, we conducted age group-stratified analyses (Table 4). A history of chronic conditions was strongly associated with higher testing rates, with the size of the effect being the largest among infants

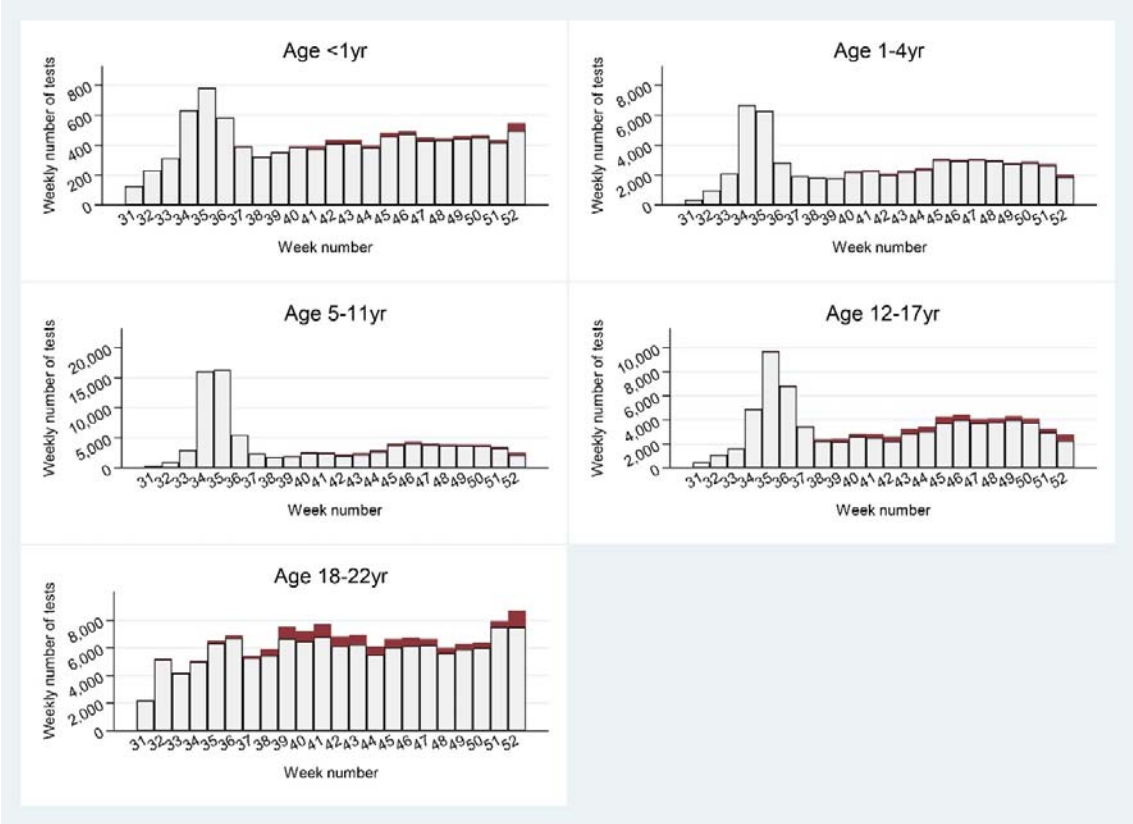

Figure 2 Weekly number of tests (white bars) and positive results (red bars) stratified by age group (weeks 31-52, 2020)

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Table 3 Results of models adjusted for age group, sex, socio-economic position and history of chronic conditions

	Testing*		PCR confirmed infection**		Admission***	
	Adj IIR	95%CI	Adj HR	95%CI	Adj HR	95%CI
AGE GROUP						
<1year	1	-	1	-	1	-
1-4 years	1.22	1.20, 1.24	0.76	0.68, 0.84	0.13	0.09, 0.19
5-11 years	1.07	1.05, 1.09	1.31	1.19, 1.44	0.11	0.08, 0.15
12-17 years	1.23	1.20, 1.25	3.12	2.85, 3.42	0.13	0.10, 0.19
18-22 years	2.04	2.00, 2.08	4.08	3.73, 4.47	0.29	0.22, 0.40
SEX						
Male	1	-	1	-	1	-
Female	1.17	1.16, 1.17	1.05	1.02, 1.08	1.14	0.91, 1.42
Socio-economic position (SEP)						
High	1.03	1.01, 1.04	1.19	1.13, 1.24	0.57	0.36, 0.89
Middle	1.03	1.02, 1.04	1.12	1.09, 1.16	0.82	0.65, 1.03
Low	1	-	1	-	1	-
CHRONIC CONDITIONS						
None	1	-	1	-	1	-
One	1.28	1.27, 1.30	0.79	0.75, 0.85	2.79	1.98, 3.94
More than one	1.63	1.56, 1.70	0.570	0.58, 0.84	13.09	8.46, 20.27

Footnotes:

* Wald test for interaction: age and sex p<0.0001; age and NS-SEC p<0.0001; age and chronic conditions p<0.0001;

**interaction: age and sex p<0.0001 , age and SEP p<0.0001 , age and chronic conditions p=0.0004; global test to check proportionality assumption p<0.0001 (for age, SEP, chronic conditions).

*** interaction: age and sex p= 0.045 , age and NS-SEC p= 0.94 , age and chronic conditions p =0.26; global test to check proportionality assumption p 0.0009 (for age, chronic condition

Table 4 Incidence Risk Ratios of being tested by age group mutually adjusted for sex, socio-economic position and history of chronic conditions

	Age <1 year		Age 1-4 years		Age 5-11 years		Age 12-17 years		Age 18-22years	
			N		N		N		N	
Number of CYP in model	98333		216,048		397751		326249		317625	
N events	9509		59176		92007		79771		137939	
	Adj IIR	95%CI	Adj IIR	95%CI	Adj IIR	95%CI	Adj IIR	95%CI	Adj IIR	95%CI
SEX										
Male	1	-	1	-	1	-	1	-	1	-
Female	0.88	0.85, 0.91	0.90	0.89, 0.92	0.90	0.89, 0.91	1.20	1.18, 1.22	1.61	1.58, 1.63
Socio economic position										
High	1.59	1.52, 1.67	1.32	1.28, 1.35	0.96	0.94, 0.99	0.90	0.88, 0.93	0.93	0.91, 0.96
Middle	1.23	1.18, 1.27	1.11	1.09, 1.13	1.01	0.99, 1.02	0.99	0.97, 1.01	1.01	0.99, 1.03
Low	1	-	1	-	1	-	1	-	1	-
CHRONIC CONDITIONS										
None	1	-	1	-	1	-	1	-	1	-
One	1.97	1.81, 2.15	1.30	1.25, 1.34	1.39	1.35, 1.43	1.37	1.32, 1.42	1.11	1.08, 1.13
More than one	3.53	3.20, 3.89	1.92	1.75, 2.10	2.13	1.95, 2.33	1.63	1.47, 1.80	1.12	1.05, 1.20

PCR-confirmed infections

Among the 378,402 PCR tests identified in the cohort, 20,003 (5.3%) were positive and 7,275 (1.9%) were void. Excluding multiple positive tests per CYP, this corresponds to 19,005 PCR confirmed index infections in 7.4% (19,005/ 256,741) of the CYP who were tested between 1st August 2020 and 31st December 2020.

The overall rate of PCR-confirmed infections was 179.4 (95% CI 176.9-182.0) per 1,000 CYP-years. Young adults (aged 18-22 years) had the highest rates of PCR-confirmed infections and those aged 1-4 years the lowest (Appendix Table 4 & 5). Infants had the highest PCR-confirmed infection rates in preschool children, otherwise infection rates were positively correlated with age. Among the infants who tested positive 20.3% (56/276) were aged <3months and 38.8% (107/276) aged <6months. Overall, CYP from higher SEP groups and those with no history of chronic conditions had a higher risk of PCR-confirmed infection (Table 3). As we identified statistically significant interaction terms between age group and each of the other main risk factors, we conducted stratified analyses by age group (Table 5). These results showed that among infants and preschool children, PCR-confirmed infection rates were lower among higher SEP groups, whereas among CYP aged 12 and above, children from higher SEP groups were more likely to be infected. Infants with chronic conditions had higher infection rates than those without; the opposite was true for CYP aged ≥12 years.

Additional analyses suggested that children aged <5 years with one older sibling had a reduced risk of a PCR confirmed infection compared to children with no older siblings (HR 0.63 (95%CI: 0.49-0.81) and 0.86 (95%CI: 0.76-0.98) for infants and 1-4 year olds, respectively, Appendix Table 6). Further, in children aged 12-17 years, being overweight/obese increased the risk of a PCR-confirmed infection compared to being of normal BMI (HR: 1.07 (95%CI: 1.00-1.15), Appendix Table 6).

Table 5 Time to PCR confirmed infection: hazard ratios (HR) by age group mutually adjusted for sex, socio-economic position and history of chronic conditions

	Age <1 years		Age 1-4 years		Age 5-11 years		Age 12-17 years		Age 18-22 years	
Number of CYP in model	9661		49288		70245		76262		70212	
Number of PCR confirmed infections	276		1114		1286		2706		4338	
	AdjHR	95%CI	AdjHR	95%CI	AdjHR	95%CI	AdjHR	95%CI	AdjHR	95%CI
SEX										
Male	1	-	1	-	1	-	1	-	1	-
Female	1.16	0.94, 1.42	1.08	0.97, 1.21	1.11	1.03, 1.19	1.20	1.14, 1.26	0.95	0.91, 0.99
SOCIO-ECONOMIC POSITION										
High	0.70	0.49, 0.99	0.76	0.64, 0.92	0.86	0.75, 0.99	1.11	1.02, 1.20	1.52	1.43, 1.63
Middle	0.99	0.80, 1,24	0.99	0.88, 1.11	1.08	1.00, 1.17	1.13	1.07, 1.19	1.14	1.09, 1.19
Low	1	-	1	-	1	-	1	-	1	-
CHRONIC CONDITIONS										
None	1	-	1	-	1	-	1	-	1	-
One	1.03	0.56, 1.88	0.80	0.63, 1.02	0.96	0.82, 1.14	0.86	0.77, 0.97	0.78	0.71, 0.84
More than one	2.04	1.08, 3.82	0.71	0.39, 1.29	0.86	0.52, 1.44	0.80	0.57, 1.13	0.42	0.41, 0.73

COVID19-related-hospital admissions

Between 1st February 2020 and 31 December 2020, 55,940 CYP in the cohort were admitted to hospital at least once, accounting for 81,312 admissions. Of these admissions, 346 (0.6%) in 318 CYP were identified as COVID-19-related admissions. 25 CYP were admitted more than once. The median time to re-admission was 5 (IQR 2-12) days. The median length of stay was 2 days (IQR 1-4 days). There were 110 admissions between February and July (31.8%) and 236 (68.2%) between August and December (Figure 3).

Of the 346 COVID-19-related admissions 203 (58.7%) had a U07.1/U07.2 recorded as primary diagnosis and 258 (74.6%) were temporally associated with a SARS-CoV-2 positive test with or without a primary or secondary U07.1/U07.2 diagnosis (Figure 4).

The overall COVID-19 related admission rate was 29.4/100,000 (95%CI 26.3-32.8) CYP years. Infants had the highest COVID-19 related admission rate across the age groups: 120.6/100,000 (95%CI 92.2-157.9). CYP with more than one chronic condition type recorded had the highest admission rates across all age groups (Appendix table 7 & 8). Overall, 12.0% (*n*=38) of the 318 CYP admitted had at least one type of chronic condition, and 6.9% (*n*=22) had multiple types of chronic conditions recorded; thus 88% of admitted CYP did not have an underlying chronic condition.

Of the CYP with chronic conditions who had a COVID-19 related admission, neurological/sensory conditions were the common condition type recorded among children aged<12 years, whereas among those aged 12-22 years the most common conditions were developmental/mental health conditions followed by metabolic/gastrointestinal/endocrine/genitourinary conditions.

Across all ages, presence of one or more chronic condition increased the risk of COVID-19-related admissions and CYP from lower SEP groups had the highest risk of COVID-19-related admission (Table 3). We identified statistically significant interaction terms between age group and each of the other main risk factors, and therefore conducted age-stratified analyses (Table 6). Having more than one chronic condition remained the strongest risk factor for COVID-19-related admission across all age groups. There was no statistically significant association between prematurity, number of older siblings, or BMI category and COVID-19 related hospital admission risk (Appendix Table 9).

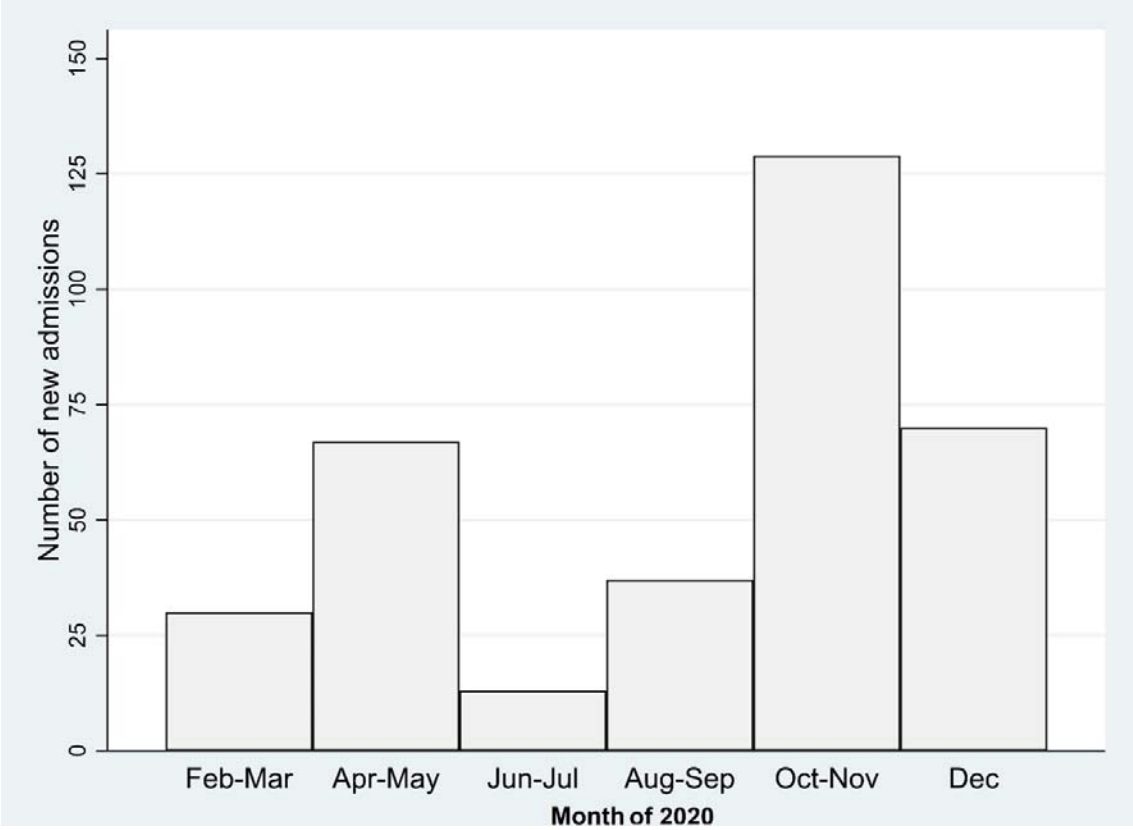
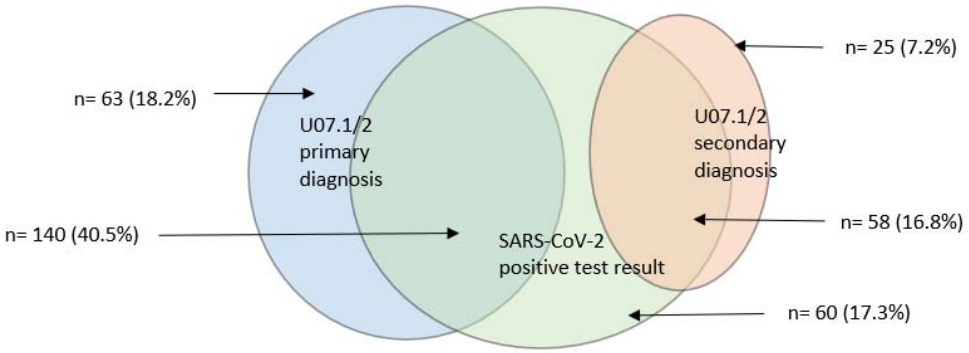


Figure 3 Monthly number of COVID-related hospital admissions (week 5-52, year 2020; 1st February 2020 to 31st December 2020)



348

349 **Figure 4** Number of COVID-related admissions temporally associated with PCR positive test
350 up to 14 days before admission and by primary and secondary COVID19 diagnosis
351 (U07.1/U07.2) Total admissions (*n*)= 346

352

353

Table 6 Time-to-COVID related admissions: hazard ratios (HR) by age group mutually adjusted for sex, socio-economic position and history of chronic conditions

	Age <1 year		Age 1-4 years		Age 5-11 years		Age 12-17 years		Age 18-22 years	
Number of CYP in model	92,530		251,884		347,542		385,664		268,467	
N Admissions	53		51		55		49		110	
	AdjHR	95%CI	AdjHR	95%CI	AdjHR	95%CI	AdjHR	95%CI	AdjHR	95%CI
SEX										
Male	1	-	1	-	1	-	1	-	1	-
Female	0.81	0.51, 1.29	1.40	0.83, 2.36	0.96	0.54, 1.70	1.09	0.69, 1.72	1.47	0.99, 2.17
Socio-economic position										
High	0.47	0.18, 1.19	0.47	0.17, 1.34	0.90	0.34, 2.38	0.31	0.10, 1.01	0.62	0.26, 1.45
Middle	0.82	0.51, 1.32	0.68	0.40, 1.17	0.91	0.49,1.66	1.02	0.64, 1.63	0.74	0.50, 1.09
Low	1	-	1	-	1	-	1	-	1	-
CHRONIC CONDITIONS										
None	1	-	1	-	1	-	1	-	1	-
One	1.37	0.34, 5.60	1.43	0.52, 3.98	3.30	1.40, 7.80	3.16	1.51, 6.61	3.75	2.34, 5.99
More than one	17.92	7.21, 44.55	12.87	5.12, 32.40	12.33	2.97, 51.17	20.93	9.03, 48.53	8.16	3.56, 18.75

ICU admissions and PIMS-TS cases

Thirteen (3.8%) of the 346 COVID-related admissions involved an ICU attendance, accounting for 1.2% of the 1,238 ICU admissions in CYP during the study period. Around half of these admissions were in CYP with a history of one or more types of chronic conditions. The median age of CYP admitted to ICU was 14 years (IQR 9-19 years) and the median length of stay at ICU was 6 days (IQR 2-7 days). Half of COVID-related ICU admissions were in boys.

We identified less than five admissions with a diagnosis suggestive of PIMS-TS and temporally associated with a positive PCR test (<28 days prior admission by definition), all in males with an age spanning from 9 to 14 years. The median length of stay at admission was 10 days (IQR 6-14).

Sensitivity analyses

Among the 346 COVID related admissions, 199 (57.5%) were emergency admissions with a primary diagnosis of U07.1/U07.2. Using the more specific definition, the COVID-19 related hospital admission rates were 107.0 (95% CI 80.4-142.4), 13.4 (9.0-19.8), 8.0 (5.6 – 11.7), 9.3 (6.3-13.6) and 27.7 (21.6-35.5) per 100,000 CYP years in age groups <1, 1-4, 5-11, 12-17 and 18-22 years respectively (Appendix Table 10 &11). This is 1.8 to 2 times higher than the more inclusive definition for CYP aged ≥1 year. Refitting the Cox proportional hazard models by age using the specific definition confirmed that presence of one or more chronic conditions remained the only significant risk factor for hospital admission (Appendix Tables 12 & 13). The median length of stay remained 2 days (IQR 1-5).

Discussion

Over one fifth of CYP in Scotland had at least one SARS-CoV-2 PCR test during 2020, and 1.5% had a PCR-confirmed infection. Testing rates increased with increasing age. PCR-confirmed infection rates were highest in 18–22-year-olds, followed by secondary school children and infants. CYP with chronic conditions were more likely to be tested, but CYP with chronic conditions of secondary school age or older were less likely to have a PCR confirmed infection. Whilst COVID-19 related hospital admissions were uncommon (less than 3 per 10,000 CYP admitted in 2020), infants and those with multiple types of chronic conditions recorded had the highest COVID-19 related-admission rates. Preschool children from lower SEP groups were more likely to have PCR-confirmed infection, and secondary school children and young adults from lower SEP groups less likely. Across all ages, SEP was significantly associated with COVID-related hospital admission. We identified no

391 statistically significant associations between prematurity, nor BMI and COVID-related
392 admission risk; however the number of children admitted was small.

393 The well-established Scottish data linkage infrastructure allowed us to include data for all
394 CYP born in Scotland since 1997, thereby minimising selection bias and loss to follow-up.
395 We relied on linkage between hospital admission and public health surveillance data to
396 define COVID-19-related admissions, allowing us to examine the robustness of our
397 definitions in the linked data, rather than only relying on time difference between SARS-CoV-
398 2 positive test and hospital admission alone. Importantly, by using a national birth cohort for
399 this study, we could examine variations in population-based rates of SARS-CoV-2 testing,
400 PCR confirmed infections and COVID-19-related hospital admissions across the full CYP
401 age range, rather than only examining risk factors for ICU admission and death in
402 hospitalised children. Using a population-wide study sample also minimises the risk of
403 collider bias[28] which may risk validity in studies only including hospitalised patients.

404 Despite the use of a national birth cohort, we were unable to determine risk factors for rarer
405 outcomes including COVID-19-related ICU admission and cases of PIMS-TS. Pooling results
406 across multiple countries with data linkage capabilities allowing national CYP birth cohorts to
407 be created, could provide reliable risk estimates for these more severe outcomes following
408 SARS-CoV-2 infection in CYP.

409 Further, this study included data from the first year of the pandemic, when wildtype (until
410 November 2020), followed by Alpha (dominant from December 2020) SARS-CoV-2 variants
411 were circulating in Scotland. This study will need to be repeated to examine the impact of
412 new circulating variants, including Delta and Omicron, and changing transmission dynamics
413 as vaccination of adults appear to be concentrating virus circulation among younger age
414 groups.[29] Recommendations to vaccinate high risk children aged 12 years and older against
415 SARS-CoV-2 with two doses of Pfizer-BioNTech (BNT162b2; COMIRNATY) COVID vaccine
416 was introduced in July 2021 in the UK; prior to this only children aged 12 and older with
417 severe neurodisability, and 16-17 year olds with underlying conditions were recommended
418 vaccination.[30] In August and September 2021, these recommendations changed to advise
419 vaccination with one dose for all 16-17 olds (due to risk of myocarditis), and then all children
420 aged 12 years and above respectively.[31 32] The US Food and Drug Administration approved
421 the Pfizer-BioNTech vaccine for use in 5-11 year olds in late October 2021. Vaccination of
422 children is likely to change risks of hospital admission, particularly among children with
423 multiple chronic conditions. Whilst the benefits of vaccines may extend to non-health
424 domains (e.g. school absences), further studies will need to examine whether the COVID-19
425 vaccination programme has amended the admission risks reported in this study. However,

the results reported here provide a baseline during the first pandemic year against which more recent data can be compared.

We based our classification of chronic conditions on coded information in SMR-01 and SBR records; this may mean we have missed some conditions that are primarily managed in primary or community care settings. Our classification of socio-economic position was based on parental occupation derived from birth certificates, however, particularly among older CYP this may not reflect current socio-economic circumstances.

We highlight that infants have the highest admission risk among CYP, despite higher testing rates in older children and young adults. A previous systematic review (preprint) has indicated that infants are also at highest risk of requiring PICU admission once in hospital with COVID-19 disease.[14] However, admission rates in infancy related to SARS-CoV-2 (1/1000 child-years) is lower than admission rates associated with confirmed influenza (2/1000 child-years)[33] or respiratory syncytial virus infections (22/1000-child years).[34] Future research should examine how COVID-19 vaccination programmes for pregnant women and older children, and removal of non-pharmaceutical interventions to control population mixing, affect infant SARS-CoV-2 admission rates.

We demonstrated that a history of chronic conditions, and particularly living with multiple different types of chronic conditions, was the most prominent risk factor for COVID-19 related hospital admission rates among CYP, however the vast majority of admitted children had no chronic conditions recorded. Children with chronic conditions also experience higher hospital admission rates for other conditions and injuries.[35] CYP with chronic conditions were more likely to be tested than those without, however in older age groups CYP with chronic conditions were less likely to be positive. This may reflect lower threshold for testing among high-risk groups.

Preschool children from lower SEP groups (indicated by parental occupation recorded on the birth certificate) had higher risks of PCR-confirmed infection than children from higher SEP groups. This may be because younger children are spending more time in the home with their parents, and their risk of infection is therefore more strongly associated with their parents' occupation (and ability to work from home). In older CYP, we instead identified higher PCR-confirmed infection rates among higher SEP groups, despite lower testing rates. This may be due to CYP from lower SEP groups being less likely to attend post-16 education, including university. Large outbreaks occurred in universities in Scotland in the autumn of 2020, which led to a surge in case numbers in 18-22 year olds.[36] Linkage between SARS-CoV-2 test results, hospital admission and education data are required to

460 confirm whether exposure in education settings can explain these differences in infection
461 risk.

462 Low SEP at birth was also a risk factor for COVID-19-related admission in CYP in the overall
463 model (incorporating all ages). This confirms previous reports which have indicated higher
464 risk of severe outcomes in hospitalised adult COVID patients from more deprived areas,[37]
465 and higher all-age hospital admission rates in areas with higher area deprivation scores.[38 39]
466 Although we did not identify SEP as a significant risk factor for admission in age group
467 specific models, COVID-19 related admission rates in children are much lower than in
468 adults. Therefore, systematic differences in admission rates by SEP among specific age
469 groups of CYP are harder to detect, even when using national data.

470 Our results showing that COVID-19 related admission rates in CYP peak in infancy indicates
471 that further research and efforts to prevent COVID-19 admissions in children should include
472 a focus on this age group. Pregnant women in Scotland are recommended to receive two
473 doses of Pfizer/BioNTech COVID-19 vaccine. [40] As for pertussis[41 42] and influenza,[43 44]
474 maternal vaccination during pregnancy could protect young babies from SARS-CoV-2
475 infection, however no studies to date have examined this. Further, given that CYP with
476 chronic conditions are more likely to be admitted to hospital admission with COVID-19
477 disease than other CYP, studies monitoring the effectiveness of COVID-19 vaccines against
478 severe outcomes in these high-risk groups are required to determine whether vaccination
479 reduces the risk of admission.

480 We identified a peak in COVID-19-related hospital admissions in infants, and presence of
481 chronic conditions as the strongest risk factor for hospital admissions in CYP, although the
482 majority of admitted children did not have chronic conditions recorded. Further studies are
483 urgently needed to examine whether maternal vaccine during pregnancy prevents COVID-19
484 admissions in infants. These data also provide baseline risks of infection and hospital
485 admission for risk-benefit assessments of childhood vaccination, particularly for preschool
486 children.

487

Ethics statement

This study was approved by the University of Edinburgh School of Geosciences Ethics Committee (reference number 2020-401) and the Public Benefit and Privacy Panel for Health and Social Care (reference 1819-0049).

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Conflicts of interest

None

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